PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference AM-101457PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US2004/033058	International filing date *(day/month/year)* 30.09.2004	Priority date *(day/month/year)* 01.10.2003
International Patent Classification (IPC) or national classification and IPC A61K9/16, A61K9/28, A61K47/32, A61K47/38, A61K47/14, A61K31/4439, A61K9/00		
Applicant WYETH		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 5 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.05.2005	11.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Hornich, E Telephone No. +49 89 2399-8721

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/033058

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-24 as originally filed

   Claims, Numbers

   1-30 filed with telefax on 20.09.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 10
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/033058

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 22 (with regard to industrial applicability)

because:

☒ the said international application, or the said claims Nos. 22 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/033058

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-30
Industrial applicability (IA)	Yes:	Claims	1-21, 23-30
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

SECTION I

1. The amendments filed with the fax of 20/09/05 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following:

   Claim 10:
   '48% w/w' has been introduced into the claim.
   This value is not disclosed in the application documents as originally filed.
   The table on p. 22 discloses a value of 48.67 % w/w. This value is however disclosed in a particular example.

   The amended claim 10 will not be taken into account for the establishment of the International Preliminary Report on Patentability.
   Claim 10 will be considered as originally filed, i.e. originally filed claim 11.

SECTION III

2. Claim 22 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

SECTION V

3. *References*:

   D1: WO 96/01624 A
   D2: US-A-6 159 499
   D3: US-B1-6 365 184
   D4: US-A-5 997 903

4. *Novelty* **(Art. 33(2) PCT)**

4.1 **D1**discloses enteric-coating-layered units of core material containing e.g. pantoprazole compressed into a tablet.
'The multiple unit tableted dosage form may be dispersed in an aqueous liquid and can be given to patients with swallowing disorders and in pediatrics. Such a suspension of dispersed enteric coating layered units of appropriate size can be used for oral administration and also for feeding through a naso-gastric tube.' (p. 9, l. 23-27).
The active may be formulated into a core material by extrusion / spheronization. The size of the formulated core material is between 0.1 and 4 mm, preferably between 0.1 and 2 mm. Binders, disintegrating agents and surfactants can be used (see p. 12, l. 9 and p. 11, l. 19-26).
Before applying enteric coating layer(s) onto the core material in the form of individual pellets, said pellets may optionally be covered with one or more separating layers. The material for separating layers can e.g. be *hydroxypropyl methylcellulose* (hypromellose) (p. 13).
Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s) (e.g. HPMC, p. 15/16).
(see in particular *example 2* in combination with the general disclosure of **D1**. Example 2: core size: 0.5 mm).
The amount of the over-coating layer in the examples falls within the ranges of claim 3.

The average size of the coated multiparticulates of about 1 mm in diameter is not explicitly disclosed in **D1.**

4.2 **D2** discloses multiparticulates which have
a core which comprises a plurality of nuclei and an active principle, e.g. pantoprazole, mixed together;
an intermediate layer surrounding the core (e.g. HPMC), and
an enteric layer surrounding the intermediate layer (e.g. methacrylic acid polymer).

The core is prepared by e.g. granulation; polysorbate 80 or sodium lauryl sulfate are added (col. 6, l. 7-36).

The composition may be in form of micro-tablets enclosed inside a capsule (col. 7, l. 37). The average size of the coated multiparticulates of about 1 mm in diameter is not explicitly disclosed; however, it is disclosed that a capsule may contain e.g. 16 micro-tablets (col. 7, l. 48); therefrom, it appears that the size of the micro-tablets corresponds to the size of the particulates of the present application.

4.3 **D3** discloses enteric coating multiparticulates of e.g. *pantoprazole* which may be filled into a capsule, tableted to obtain a multiple unit dosage form or dispersed in an aqueous liquid to be fed trough a naso-gastric tube.
The proton pump inhibitor may be formulated into a core material (pref. 0.1 - 2 mm, 1mm: see col. 27, l. 17) with excipients, e.g. binders, surfactants by extrusion / spheronization. Binders are e.g. cellulosics or PVP; sodium lauryl sulfate is mentioned as suitable surfactant (col. 9).
A separating layer (e.g. HPMC) may be applied onto the cores before covering with an enteric coating (e.g. methacrylic acid copolymers). An over-coating layer may also be applied.
(See the general disclosure and in particular *examples 3, 12 and 17*).

The average size of the coated multiparticulates of about 1 mm in diameter is not explicitly disclosed.

4.4 The subject-matter of claims 1-30 appears therefore ***novel*** over the cited prior art.

5. *Inventive Step* **(Art. 33(3) PCT)**

The present claims are novel over **D1**, **D2** or **D3** as the average size of the coated multiparticulate of about 1 mm in diameter is not explicitly disclosed in the prior art documents.
However, the particle size which is claimed in the present application falls within the ranges of the particulates that are disclosed in the above-cited prior art documents (see '*Novelty*').

In view of the teaching of the cited prior art documents, no inventive merit can be seen in the selection of the particular average size of the coated multiparticulate of about 1 mm in diameter.

The subject-matter of claims 1-30 can therefore ***not*** be considered ***inventive***.

6. *Industrial Applicability* **(Art. 33(4) PCT)**

6.1 The requirements of industrial applicability would be fulfilled for the subject-matter of claims 1-21 and 23-30.

6.2 For the assessment of the present claim 22 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VI

7. *Certain published documents*

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2004098577	18/11/2004	07/05/04	08/05/03

WO2004098577 discloses pellets comprising pantoprazole and various coatings.

CLAIMS:

1. Pantoprazole multiparticulates having reduced release under gastric conditions and fast release at neutral pH, wherein each of said multiparticulates comprises:

a spheroid core comprising pantoprazole or an enantiomer thereof, or a salt or hydrate thereof, at least one surfactant, at least one distintegrant, and about 1% to about 2% w/w water;

an initial seal coat on the spheroid core;

an enteric coat on the core, said enteric coat comprising a copolymer of methacrylic acid and methacrylates in the range of about 15 to about 45 % w/w of each of the multiparticulates; and

wherein said coated multiparticulates have an average size of about 1 mm in diameter.

2. The pantoprazole multiparticulates according to claim 1, further comprising a final seal coat on the enteric coat.

3. The pantoprazole multiparticulates according to claim 2, wherein the final seal coat comprises about 0.1 to 10 wt% of the multiparticulates.

4. The pantoprazole multiparticulates according to claim 2 or claim 3, wherein the final seal coat comprises hydroxypropyl methylcellulose (hypromellose).

5. The pantoprazole multiparticulates according to claim 1 wherein said said initial seal coat is in the range of about 2 to 4 % w/w of the weight of the uncoated core.

6. The pantoprazole multiparticulates according to any of claims 1 to 5, wherein the initial seal coat comprises hypromellose.

7. The pantoprazole multiparticulates according to any one of claims 1 to 6, wherein the surfactant comprises from about 2 to about 7% by weight of the uncoated core.

8. The pantoprazole multiparticulates according to any one of claims 1 to 7, wherein the surfactant is a polysorbate.

9. The pantoprazole multiparticulates according to claim 8, wherein the polysorbate is polysorbate 80.

10. The pantoprazole multiparticulates according to any one of claims 1 to 9, wherein the enteric coat comprises 27.5 to 48% w/w of the multiparticulate.

11. The pantoprazole multiparticulates according to claim 1, wherein the enteric coating comprises about 30% w/w of Eudragit L 30 D-55 coating, about 15% w/w talc, about 3% triethyl citrate and a pH adjuster; said amounts being by weight of the multiparticulate.

12. The pantoprazole multiparticulates according to any one of claims 1 to 11, wherein the pantoprazole compound is present in the range of from about 5 to 50 w/w, of the spheroid core.

13. The pantoprazole multiparticulates according to any one of claims 1 to 12 , in which the core comprises pantoprazole compound in an amount equivalent to about 40 mg pantoprazole per 100 mg uncoated multiparticulate.

14. The pantoprazole multiparticulates according to any one of claims 1 to 13, wherein said spheroid core further comprises a pH adjuster and hypromellose.

15. The pantoprazole multiparticulates according to any of claims 1 to 14, wherein the disintegrant is selected from the group consisting of microcrystalline cellulose and crospovidone, and mixtures thereof.

16. The pantoprazole multiparticulates according to claim 15, wherein the microcrystalline cellulose comprises about 25 to about 30% by weight of the core.

17. The pantoprazole multiparticulates according to claim 15 or claim 16, wherein the crospovidone comprises about 14 to about 16% by weight of the core.

18. The pantoprazole multiparticulates according to claim 1, wherein the spheroid core consists essentially of:

pantoprazole sodium sesquihydrate	45 % w/w
microcrystalline cellulose	27 % w/w
polysorbate 80	5 % w/w
crospovidone.	15 % w/w
hypromellose 2208	1 % w/w and
sodium carbonate	7 % w/w.

19. A pantoprazole formulation for use in dosing to pediatric patients, said formulation comprising a suspension comprising the pantoprazole multiparticulates of any one of Claims 1 to 18 and a physiologically compatible suspending liquid.

20. A capsule comprising the pantoprazole multiparticulates of any one of Claims 1 to 19.

21. A foil packet comprising the pantoprazole multiparticulates of any one of Claims 1 to 19.

22. A method of treating humans in need of pantoprazole, said method comprising the step of administering an effective dose of the pantoprazole multiparticulates of any one of Claims 1 to 19.

23. A method of producing a multiparticulate formulation of pantoprazole, said method comprising the steps of:

producing a spheroid core comprising pantoprazole or an entantiomer thereof, or a salt thereof, a surfactant, a distintegrant, via extrusion and spheronization, said core containing about 1 to about 2% w/w water;

applying an initial seal coat to the spheroid core, said seal coat being about 1 % w/w to about 2 % w/w of the multiparticulate;

applying an enteric coating over the initial seal coat, said enteric coating comprising a copolymer of methacrylic acid and methacrylates in an amount that provides the multiparticulate with 15 to 45 % w/w dry enteric coating polymer; and

optionally applying a final seal coat to the enteric-coated spheroid core, said final seal coat being about 1 wt% of the multiparticulate;

wherein said multiparticulates have an average size of no greater than about 1mm in diameter.

24. The method according to claim 23, wherein the spheroid core is prepared by mixing the ingredients in a low shear mixer at low shear conditions at a range of about 25 rpm to 35 rpm.

25. The method according to claim 24, wherein the low shear conditions are 32 rpm.

26. The method according to claim 24 or claim 25, wherein the spheroid cores are dried at a low temperature not exceeding about 40°C for a period of 8 to 72 hours to a percent (%) loss-on-drying (LOD) of 3.4% to 4.3%.

27. The method according to claim 23, further comprising the step of applying an layer of talc in an amount of 0.05% w/w to 0.1% w/w of the multiparticulate.

28. The method according to claim 23, wherein the enteric coating is sprayed as a suspension onto the spheroid core.

29. Use of pantoprazole multiparticulates according to any of claims 1 to 19 in preparing a medicament.

30. A composition comprising an oral dosage form containing an effective amount of a pantoprazole multiparticulate wherein, after oral administration thereof to a subject, the pantoprazole has a Cmax ratio of 62 to 66 ng/mL and an AUC ratio of 89 to 94, for a 40 mg unit dose of pantoprazole.